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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/550,516	05/26/2006	Staffan Stromblad	P07900US01/BAS	4509

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EXAMINER	
PACKARD, BENJAMIN J	
ART UNIT	PAPER NUMBER
1612	
MAIL DATE	DELIVERY MODE
12/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,516	STROMBLAD ET AL.	
	Examiner	Art Unit	
	Benjamin Packard	1612	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11* is/are pending in the application.

4a) Of the above claim(s) *1,2 and 6-11* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's request for reconsideration of the finality of the rejection of the last Office action is persuasive and, therefore, the finality of that action is withdrawn.

Applicants' arguments, filed 11/18/09, have been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claim Rejections - 35 USC § 112- Written Description

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The first paragraph of 35 USC 112 requires that the specification contain a written description of *the invention*. Accordingly, where a particular compound has not been *specifically* named or "otherwise exemplified", one is left to select from mere *possibilities* encompassed by the broad disclosure, with no guide indicating or directing that this particular selection should be made rather than any of the many others which

could also be made. In re Ruschig, 154 USPQ 118, 122 (CCPA 1967). As elaborated by the court:

> Specific claims to single compounds require reasonably specific supporting disclosure and while we agree with the appellants, as the board did, that *naming* is not essential, something more than the disclosure of a class of 1000, or 100, or even 48, compounds is required. Surely, given time, a chemist could name (especially with the aid of a computer) all of the half million compounds within the scope of the broadest claim, which claim is supported by the broad disclosure. This does not constitute support for each compound individually when separately claimed.

Here, the instant claim broadly recites a compound which is only nominally identified by the term "prodrug" thereof, but not a specific structure. The only compound particularly described by the instant specification are those set forth at pages 2-4, which do not describe the "prodrug" form of the compound; no others appear to be "specifically named or otherwise exemplified". Accordingly, the claimed subject matter is not adequately described by the specification as originally filed.

Claim Rejections - 35 USC § 112 – Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 3-5 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treatment of malignant melanoma with PRIMA-1, does not reasonably provide enablement for treatment of malignant melanoma with the broader class of compounds instantly claimed or the inhibition of undesired angiogenesis. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

To be enabling, the specification of the patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557, 1561 (Fed. Cir. 1993). Explaining what is meant by "undue experimentation," the Federal Circuit has stated:

> The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the claimed invention. PPG v. Guardian, 75 F.3d 1558, 1564 (Fed. Cir. 1996).[1]

The factors that may be considered in determining whether a disclosure would require undue experimentation are set forth by In re Wands, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) the quantity of experimentation necessary,
2) the amount of direction or guidance provided,
3) the presence or absence of working examples,
4) the nature of the invention,
5) the state of the prior art,
6) the relative skill of those in the art,
7) the predictability of the art, and
8) the breadth of the claims.

These factors are always applied against the background understanding that scope of enablement varies inversely with the degree of unpredictability involved. In re

Fisher, 57 CCPA 1099, 1108, 427 F.2d 833, 839, 166 USPQ 18, 24 (1970). Keeping that in mind, the Wands factors are relevant to the instant fact situation for the following reasons:

1. The nature of the invention, state and predictability of the art, and relative skill level

The invention relates to treatment of disease, particularly treating cancer. The relative skill of those in the art is high, that of an MD or PHD. That factor is outweighed, however, by the unpredictable nature of the art. As illustrative of the state of the art, the examiner cites Gupta (Postgrad. Med. J. 2005;81 ;236-242) where undesired angiogenesis is tested in experimental rodent models, most results don't translate into predictable clinical trials (pg 239 Limitations of Angiogenesis Based Treatments). Examiner also cites with regard to cancer treatment Suggitt and Bibby, *Clinical Cancer Research*, Vol 11, 971-981. Suggitt and Bibby teaches the unpredictability of treating cancer. Note however, that the current human tumor cell line in vitro screen is generally unpredictable. Modern methods are susceptible to false-positive and false-negative results. (page 973 1st paragraph on right-hand column). Difficulty in determining results leads to difficulty in testing for effectiveness of compounds, which leads to unpredictability in treating cancers. Finally, Examiner also cites Satyamoorthy et al (Trends in Molecular Medicine Volume 7, Issue 5, 1 May 2001, Pages 191-194) which

[1] As pointed out by the court in In re Angstadt, 537 F.2d 498 at 504 (CCPA 1976), the key word is "undue", not "experimentation".

teaches that p53 mutations are very rare in melanoma and that the overexpression of wild-type p53 does not induce immediate cell death (pg 192, center column, first full paragraph).

2. The breadth of the claims

Inhibition/treatment of undesired angiogenesis as a general phenomenon is highly unpredictable. Further, the class of compounds for treating malignant melanomas and inhibiting angiogenesis is very large insofar as the constituents vary greatly.

3. The amount of direction or guidance provided and the presence or absence of working examples

The specification provides no direction or guidance for practicing the claimed invention in its "full scope". No reasonably specific guidance is provided concerning useful therapeutic protocols for inhibit undesired angiogenesis. Treatment of malignant melanoma with PRIMA-1 appears to be corroborated by the working examples, but there does not appear to be any evidence of the efficacy of the structural analogues, such as PRIMA-2 or PRIMA-3, let alone the broader genus of compounds claimed.

4. The quantity of experimentation necessary

Because of the known unpredictability of the art, and in the absence of experimental evidence, no one skilled in the art would accept the assertion that the instantly claimed agents could be predictably use the class of compounds instantly claimed for the treatment of malignant melanoma or to inhibit undesired angiogenesis generally, as inferred by the claim and contemplated by the specification. Accordingly, the instant claims do not comply with the enablement requirement of §112, since to practice the claimed invention in its "full scope" a person of ordinary skill in the art would have to engage in undue experimentation, with no assurance of success. Further, Examiner notes that the mechanism which Applicants appear to be claiming, i.e. activation of inactive wild-type p53, would not have predictive value for in vitro testing, given Satyamoorthy et al specifically discusses the overexpression of wild-type p53 does not lead to immediate cell death, and would not provide an expectation of success in treating malignant melanoma.

Applicant's Prior Response

Examiner notes that this rejection was previously made with regards to inhibiting undesired angiogenesis, and a response to Applicants arguments was not included in the Response dated 8/18/09. Applicants submitted a declaration under 37 CFR 1.132 by Mr. Staffan Stromblad, a co-inventor, where he discusses a link between p53 and angiogenesis in relation to a_v-integrins, which in turn is effected by the suppression of wtp53 (see pgs 2-3). Additionally, Applicants assert copending US Patent Application 10/590,054 discloses a larger number of compounds which show the desired

suppression.

Examiner disagrees. First, the instant claims, while limited in patient population, are not limited to treatment of undesired angiogenesis in malignant myeloma, but in treating undesired angiogenesis generally. Thus, a patient with malignant myeloma may also be in the need to treatment of undesired angiogenesis in additional cancers which the instant compound would not have a reasonably expectation of success with.

Second, the limited number of compounds shown to have any effect in vivo, does not correlate to in vitro results where the correlation of cancer treatment in vivo and in vitro is generally unpredictable. Further, there does not appear to be sufficient support for the method of either treating multiple myelomas where the only test appears to be on the WST-1 assay (see copending US Application 10/590,054 pg 26). Examiner further notes that none of the test compounds are in the scope of the instant claims where R7 and R8 are H, or where the value of "n" is modified from n=1. Additionally, the disclosure of the copending application simply illustrates assay results, but does not provide evidence that there would be an expectation of cancer treatment. Finally, there does not appear to be sufficient correlation between the assay and a specific mechanism of inhibiting undesired angiogenesis, generally.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Benjamin Packard whose telephone number is 571-270-3440. The examiner can normally be reached on M-F 8-5 EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Frederick Krass can be reached on 571-272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Benjamin Packard/
Examiner, Art Unit 1612

/Frederick Krass/
Supervisory Patent Examiner, Art Unit 1612